REMARKS

Priority

The Examiner contends that while the Applicant has submitted the required reference to the prior application, because it was submitted after the time period allotted in 37 CFR 1.78(a)(5), and as there has been no submission of the petition for unintentionally delayed claim to priority as required by 37 CFR 1.78(a)(6), Applicant has not met the conditions for priority to U.S. Provisional Application No. 60/249,173 under 35 U.S.C. § 119(e).

Applicants respectfully disagree. Applicants note that the claim for priority from U.S. Provisional Application No. 60/249,173 under 35 U.S.C. § 119(e), in addition to appearing on page 1 of the specification (albeit after the statement regarding government rights) was also stated in the Inventors' Declaration under 37 CFR 1.63, was listed in the transmittal letter for the application, and *was acknowledged by the Patent Office on the Official Filing Receipt* mailed from the Patent Office on March 20, 2002. Pursuant to MPEP 201.11(III)(D):

> "[i]f an Applicant includes a benefit claim in the application but not in the manner specified by 37 CFR 1.78(a) (e.g., if the claim is included an oath or declaration or the application transmittal letter) within the time period set forth in 37 CFR 1.78(a), the Office will not require a petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) to correct the claim if the information concerning the claim was recognized by the Office as shown by its inclusion on the filing receipt."

Since Applicants presented the claim in the application itself (albeit not on line 1), in the declaration under 37 CFR 1.63 (filed February 7, 2002) and in the application transmittal letter filed with the application, all within the time period set forth in 37 CFR 1.78(a), and since the Office recognized the claim by its inclusion on the filing receipt for the application, Applicants submit that the requirement for a petition and surcharge under 37 CFR 1.78(a) should be waived. Moreover, since Applicants have now corrected the formal requirement for the priority claim by presenting it immediately after the title on page 1, the claim to priority is now believed to be complete and proper, and Applicants respectfully request the Examiner's acknowledgment of the same.

Rejection of Claims 1-3, 8, 9, 11-15 and 29-33 Under 35 U.S.C. § 101:

The Examiner has rejected Claims 1-3, 8, 9, 11-15 and 29-33 under 35 U.S.C. § 101, contending that these claims are directed to non-statutory subject matter because the dendritic cell component of the claim could be inside a human being. The Examiner suggests that the claims be amended to recite an "isolated dendritic cell".

In order to expedite prosecution, Applicants have amended all relevant Claims to recite "an isolated dendritic cell" as suggested by the Examiner. In view of this amendment, Applicants respectfully request that the rejection be withdrawn.

Objection to the Specification and Rejection of Claims 1, 2, 3, 8, 9, 11-15, and 29-33 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has maintained a prior objection to the specification and rejection of Claims 1, 2, 3, 8, 9, and 11-15 under 35 U.S.C. § 112, first paragraph, on the basis of enablement.

Specifically, in the first part of the rejection, the Examiner responds to Applicants' prior argument that the specification is enabling for any yeast vehicle as claimed by asserting that even if it is the case that a yeast vehicle is useful on the basis that it can deliver antigens to dendritic cells (DCs) in concentrated packages that can be avidly internalized, the specification does not enable one of skill in the art to make and use any yeast vehicle other than a yeast vehicle that comprises a cell wall and a yeast spheroplast. The Examiner states that the claims read broadly on any yeast vehicle and further contends that there are no examples of any subcellular particles, which the Examiner contends includes individual yeast proteins and other constituent molecules, or guidance toward particles that would be effective in the claimed composition.

Applicants traverse this ground of rejection. Initially, Claim 1 has been amended to clarify that the yeast vehicle is selected from a whole yeast, a yeast spheroplast, a yeast cytoplast, a yeast ghost, and a subcellular yeast particle. Moreover, contrary to the Examiner's contention that a yeast subcellular particle includes individual yeast proteins and other constituent molecules, the specification clearly teaches that a "subcellular yeast particle refers to a yeast membrane that lacks a natural nucleus or cytoplasm" (see page 11, lines 3-4). Therefore, Claim 1 is limited to specific yeast vehicles and does not include individual yeast proteins. Claim 29 has been amended to recite

only the whole yeast and yeast spheroplast. Moreover, Applicants submit that the claimed invention should not be limited to the whole yeast and yeast spheroplast, as the specification provides substantial guidance to enable the making and using of the yeast cytoplast, yeast ghost and subcellular yeast particle as defined in the present specification. First, the specification defines and teaches how to make such additional yeast vehicles, with reference to publications that specifically describe the procedures for making such vehicles (see page 10, line 29, to page 11, line 8). Second, the specification is deemed to be enabling for both whole yeast and yeast spheroplasts, the latter having its cell wall removed. Applicants submit that there is no reason of record that would indicate that the other forms of the yeast vehicle set forth by the specification would not also serve to deliver antigens to DCs and thereby enhance a DC-mediated immunization process.

In the second part of the enablement rejection, the Examiner maintains the prior rejection of the claims to the extent that they read on "therapeutic" compositions. The Examiner suggests that "immunogenic" compositions are enabled. Therefore, to expedite prosecution, the claims have been amended to adopt the Examiner's suggestion and recite an immunogenic composition instead of a therapeutic composition.

In view of the foregoing amendments and remarks, the Examiner is respectfully requested to withdraw the rejection of Claims 1, 2, 3, 8, 9, and 11-15 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-3, 8, 9 and 29-33 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-3, 8, 9 and 29-33 under 35 U.S.C. § 103, contending that these claims are unpatentable over Barbera-Guillem and Paglia et al. in view of Duke (U.S. Patent No. 5,830,463). Specifically, the Examiner notes that the term yeast vehicle in the claims is interpreted as comprising a particle composed of materials from a yeast membrane. The Examiner asserts that Barbera-Guillem teaches that dendritic cells loaded *ex vivo* with antigens are effective at inducing immune responses against target cells, and that Paglia et al. teach that dendritic cells pulsed with soluble antigen *ex vivo* are able to induce both types of immune responses (CD8+ and CD4+). The Examiner therefore concludes that these references teach the administration of antigens to DCs induces immune responses, although the Examiner admits that neither reference teaches that yeast vehicles may be used for the delivery of such antigens. The Examiner contends that Duke

teaches a yeast vehicle useful in therapeutic compositions, and that these particles can be delivered to cells, including dendritic cells. The Examiner contends that the art teaches that administration of the yeast vehicles performs the same functions as the cells or soluble antigens in Barbera-Guillem and Paglia et al. and further, that the art demonstrates that the yeast vehicles are functional equivalents of the antigen delivery devices of Barbera-Guillem and Paglia et al. Therefore, the Examiner asserts that it would be obvious to use make and use the claimed compositions. Further the Examiner contends that the previously asserted unexpected results of the present invention as compared to Barbera-Guillem and Paglia et al. have not been demonstrated by evidence.

Applicants traverse the Examiner's rejection of Claims 1-3, 8, 9 and 29-33 under 35 U.S.C. § 103. First, Applicants submit that there is absolutely no suggestion or motivation in any of the references, or in the art in general, to make the combination as the Examiner has done, nor any expectation of success in combining the references.

Duke teach the a yeast vehicle that carries a heterologous antigen and its use to elicit an immune response in a mammal. At most, Duke motivate one of skill in the art to use the yeast vehicle carrying a heterologous antigen as a therapeutic vaccine. Duke teaches that yeast can deliver compounds to cell types that naturally absorb yeast, with dendritic cells being one such cell type listed among many. However, Duke does not teach the provision of a therapeutic composition comprising isolated dendritic cells that have been loaded intracellularly with a yeast vehicle and an antigen, nor the advantages of providing such a composition (discussed below). The yeast vehicle expressing an antigen is shown in Duke to elicit both a cellular and humoral immune response effectively and indeed, is set forth as a novel type of vaccine when delivered directly to an animal. Therefore, there is no motivation provided by Duke that would lead one of skill in the art to look to another reference or type of art to change the way in which the immune response is induced or to provide a different type of vaccine.

Paglia et al. teaches the conventional means of introducing soluble antigens to a DC, namely by pulsing the DC with an antigen for a period of time. Paglia et al. showed that DC cell lines pulsed with soluble antigen were able to induce a CD8+ T cell response if the DCs were transduced with or exposed to GM-CSF. The key finding in Paglia is the use of GM-CSF to mature DCs to the point where soluble antigens pulsed with the DCs may reach the MHC Class I pathway. Moreover, to

achieve results *in vivo*, the animal must be further boosted with soluble antigen after the initial vaccine. There is absolutely no teaching or suggestion in Paglia et al. to provide the antigen to the DC in any other manner, because Paglia et al. already provides a solution to put an antigen into the MHC Class I pathway (i.e., by administration of a cytokine to the DC, followed by antigen boosting *in vivo* to achieve the desired result). Indeed, Paglia et al. conclude that antigen-pulsed DCs may represent the ideal cell-based vaccine even for human tumors (see the last sentence), and therefore, does not look to additional or different solutions. Therefore, there is no suggestion or motivation to be combined with Duke or any expectation of an improvement by doing so.

Barbera-Guillem is directed to the problem that *ex vivo* loading of dendritic cells with soluble antigen has been shown to be inefficient - this reference solves the problem by utilizing immune complex-mediated uptake of an antigen by dendritic cells (i.e., via uptake of antibody complexes by Fc receptors expressed on the dendritic cells). This method requires the use of *antibodies* and a target cell (a tumor cell or a virally infected cell against which the immune response is to be generated) that is expected to shed the soluble antigen used to load the DC, so that the antibody can bind to the antigen and then be internalized by the Fc receptors on the activated dendritic cells. Therefore, this reference teaches a complete solution to a problem of *ex vivo* loading of dendritic cells that does not require any further, unrelated solution (i.e., there is absolutely no motivation in Barbera-Guillem to do anything else to the DC). Furthermore, the teachings of Barbera-Guillem are completely incompatible with the combination with Duke. For example, it is unclear to Applicants how the yeast vehicle of Duke, which is neither an antibody or equivalent thereof, would be targeted to the Fc receptors of the dendritic cell and internalized in the manner taught by Barbera-Guillem, nor would the yeast vehicle be a target cell that is the cell against which the immune response is to be directed (i.e., that contains an antigen on its cell surface that is uniquely expressed by the target cell, which it sheds as a soluble protein, all of which are features of the target cell taught by Barbera-Guillem). Furthermore, the target cell of Barbera-Guillem is restricted from physical contact with the DC (i.e., contact of the antigen is achieved by the use of an antibody).

Therefore, there is simply no suggestion, motivation or expectation of success at making and using the present invention found in the combination of Duke with either of Barbera-Guillem or Paglia et al.

Furthermore, if, as the Examiner states, the art demonstrates that the yeast vehicles of Duke are the *functional equivalent* of the antigen delivery devices of Barbera-Guillem and Paglia et al. (i.e., presumably DCs loaded with soluble antigens, unless the Examiner refers to the antibody of Barbera-Guillem which is completely different as discussed above), then again, Applicants submit that there is no motivation provided to the skilled artisan to combine a yeast vehicle of Duke with a DC of the latter two references, because there is no reason to combine functionally equivalent solutions to the same problem, particularly when none of the references provides any expectation that combining references would be operable or result in any benefit. To suggest that one of skill in the art would be motivated to combine the references because they are concerned with the same problem and achieve a similar result (e.g., are functional equivalents) is not a reasonable argument because none of Duke, Paglia et al., or Barbera-Guillem lead one to believe that there are any deficiencies in their compositions or methods that would benefit from combining the technologies (i.e., the compositions and methods of each reference provide distinct means of eliciting an immune response and are taught to be efficacious, and so there is no motivation to make changes to any of the compositions or methods). Indeed, to go beyond the teachings of any of the references and conclude that one would be motivated to combine the references can only result from a *hindsight reconstruction* using the claimed invention, which is not an appropriate standard for obviousness.

Finally, as previously discussed, the present invention provides advantages over the use of DCs with antigen alone as shown by Barbera-Guillem or Paglia et al. or even the yeast vehicles with antigen used by Duke. First, in contrast to the teachings of Paglia et al. (and therefore other teachings of loading DCs with soluble antigen), where soluble antigen must be used as a booster in order to achieve good results *in vivo*, the present invention does not require an antigen boost to achieve efficacy *in vivo*. Referring to Example 7 and Fig. 4A, for example, compositions comprising DCs carrying the yeast vehicle and antigen of the present invention were able to induce protective immunity against tumor cells expressing the antigen without the need for a booster vaccine of antigen. Second, the present invention provides additional superior and unexpected results as compared to the art cited by the Examiner. Referring to Example 4 and Fig. 2A, a composition comprising dendritic cells containing a yeast vehicle and ovalbumin antigen according to the present claims was far superior at stimulating CD8+ T cells as compared to DCs loaded with a saturating

amount of antigen (ovalbumin) alone. Example 5 and Fig. 3B compares the ability of DCs to stimulate class I-restricted antigen specific T cell proliferation using DCs pulsed with antigen alone, and two separate DC compositions encompassed by the present invention (1) DCs containing yeast vehicle and antigen, wherein the yeast vehicle and antigen are mixed together; and (2) DCs containing yeast vehicle and antigen, wherein the yeast recombinantly express the antigen. Fig. 3B shows that DC containing a mixed combination of yeast vehicle and antigen (1) resulted in a fifty-fold increase in class I-restricted antigen-specific T cell stimulation as compared to DCs pulsed with antigen alone, and the responses obtained with DCs containing yeast vehicle expressing the antigen (2) were even greater (i.e., on the basis of per molar antigen, composition (2), containing ~0.005 nM OVA at 10 yeast vehicles per DC, yielded twice the stimulation obtained with yeast vehicles mixed with 0.2 μM OVA). Furthermore, Fig. 3C shows that, as compared to DCs pulsed with antigen alone, DCs containing either composition (1) or composition (2) as discussed above resulted in greatly enhanced stimulation of MHC class II-restricted T cells. Finally, Example 7 and Fig. 4B shows that antibody production induced by the dendritic cell vaccine of the present invention was superior to the recombinant yeast vaccine alone. Therefore, the specification provides clear evidence of the unexpected and superior results achieved by the composition of the present invention over prior art DC vaccines and yeast vehicle vaccine.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 8, 9 and 29-33 under 35 U.S.C. § 103.

Rejection of Claims 1-3, 8, 9, 11-15 and 29-33 Under 35 U.S.C. § 103:

The Examiner has maintained the prior rejection of Claims 1-3, 8, 9, and 11-15 and rejected Claims 29-33 under 35 U.S.C. § 103, contending that these claims are unpatentable over Duke in view of Tomai. The Examiner contends that Duke teaches the use of yeast vehicles to deliver antigens to DC cells and that Tomai teaches the therapeutic administration of activated DCs. The Examiner states that Duke teaches that DCs may be beneficially exposed to antigens through use of the yeast vehicles such that the cells will induce both cell-mediated responses, and that, while adjuvants may not be required, that adjuvants may be used in combination with the vehicles. The Examiner further asserts that Tomai teaches that after DCs have been exposed to antigen, they may

be further exposed to additional immune response modifiers to increase the immune response. Thus, the Examiner asserts that it would have been obvious to use the yeast vehicles of Duke to deliver the antigens to the DCs of Tomai. The Examiner contends that there is no indication in the references that the two references can not be combined and also, that Applicants have not provided evidence of unexpected results.

Applicants traverse the Examiner's rejection of Claims 1-3, 8, 9, and 11-15 and rejected Claims 29-33 under 35 U.S.C. § 103. Applicants submit that the combination of references cited by the Examiner fails to suggest the present invention or provide any motivation to make the combination as the Examiner has done.

Tomai et al. teach the use of imidazoquinoline immune response modifying compounds to induce the maturation of dendritic cells *in vitro* and enhance the ability of the DCs to stimulate T cells, which can then be used directly and/or exposed to an antigen. If one turns to Tomai et al. for the motivation to make the combination as the Examiner has done, one finds that Tomai et al. fail to provide any motivation to load a yeast vehicle and an antigen into a dendritic cell, because Tomai et al. is directed to a completely different means of stimulating dendritic cells to elicit an immune response. The use of imidazoquinoline compounds is the solution that Tomai et al. provide to eliciting an immune response using DCs. There is no motivation to look to other techniques such as the provision of a yeast vehicle of the present invention and indeed, if the imidazoquinoline compound enhances the ability of the DC to present antigen, then there would be no need to look for other solutions or to provide an antigen in a different manner. The Examiner contends that Tomai teaches that after DCs have been exposed to antigen, they may be further exposed to additional immune response modifiers to increase the immune response (column 15, lines 23-55), apparently attempting to draw a connection between Tomai and a reference to adjuvants in Duke. However, Applicants find no such teaching in Tomai. This section of Tomai discusses how one may use the DCs after they have been matured using the imidazoquinoline compounds. Tomai describes exposing the matured DCs to an antigen to form a "cellular adjuvant" (i.e., the matured DC that has been exposed to an antigen is the cellular adjuvant), and then administering these DCs to a patient. No discussion of adding additional immune response modifiers to the cells is suggested, because the solution to eliciting an immune response provided by Tomai is in the exposure of the DCs to

imidazoquinoline compounds prior to exposure to antigen. Moreover, even such a suggestion does not provide any link to Duke.

As discussed above, Duke teach the use of a yeast vehicle that carries a heterologous antigen and its use to elicit an immune response in a mammal. At most, Duke motivate one of skill in the art to use the yeast vehicle carrying a heterologous antigen, as a therapeutic vaccine. There is no teaching in Duke that would lead one of skill in the art to look to another reference to change the way in which the immune response is induced or to provide a different type of vaccine because Duke teach that the yeast vehicle expressing an antigen elicits both a cellular and humoral immune response effectively when administered directly. Applicants submit that Duke and Tomai are not complementary; rather, they represent completely different solutions to eliciting an immune response, with no suggestion provided by either reference to combine the references as the Examiner has done.

Again, to suggest that one of skill in the art would be motivated to combine the references because they are concerned with the same problem and achieve a similar result (e.g., stimulation of an antigen-specific immune response) is not a reasonable argument because neither of Duke or Tomai lead one to believe that there are any deficiencies in their compositions or methods that would benefit from combining the technologies (i.e., there is no motivation to make changes to either of the compositions or methods). Indeed, to go beyond the teachings of either cited patent and conclude that one would be motivated to combine the references can only result from a hindsight reconstruction using the claimed invention, which is not an appropriate standard for obviousness.

Moreover, the present invention provides advantages over the use of DCs with antigen alone as shown by Tomai or even the yeast vehicles with antigen used by Duke. This evidence has been discussed previously herein with regard to Barbera-Guillem, Paglia et al., and Duke, and applies to this combination of references as well. The specification provides clear evidence of the unexpected and superior results achieved by the composition of the present invention over prior art DC vaccines and yeast vehicle vaccine.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 8, 9, and 11-15 and rejected Claims 29-33 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the Examiner's concerns as set forth in the September 9 Office Action, and submit that the claims are in a condition for allowance. In the event that the Examiner has any questions or concerns regarding Applicants' position, he is encouraged to contact the below named agent at (303) 863-9700 to expedite prosecution.

Respectfully submitted,

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